

I have sketched briefly the year's experience in the clinical study of pneumonia, in order to draw attention to the complexity of this disease. Fortunately, through the organized facilities of the hospital, it is now possible to determine accurately in most of the patients, the etio-logic agents concerned, and thus some order is finally emerging in regard to the classification of the cases, and the nature of the disease as a whole.

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Production and enzyme treatment of Type III pneumococcus pneumonia in monkeys. It was previously pointed out that the enzyme of bacterial origin is capable of decomposing the capsular polysaccharide of Type III pneumococcus when encountered in the animal body. Mice were infected with many lethal doses of Type III pneumococci. As late as 12 to 18 hours after the infection was established intraperitoneally, the administration of the enzyme brought about recovery in most instances. Furthermore, when the enzyme was given from 24 to 48 hours preceding the injection of many lethal doses of Type III organisms into mice, a marked protective action occurred, resulting in the recovery of most of the animals. The curative effect was shown to be due to action of the enzyme on the capsular polysaccharide, decomposing it, and thereby rendering the bacterial cells vulnerable to attack by the phagocytic cells of the animal body. This study was limited to the effect of the enzyme on an experimental infection, primarily septicemic (blood poisoning) in nature.

Later studies dealt with the action of the enzyme upon the localized infection of the skin of rabbits ("dermal pneumonia") produced by Type III pneumococcus. The lesion induced is primarily localized and is accom-

panied by septicemia of varying degrees. Again, a definite curative effect was demonstrable as shown by prompt subsidence of the skin effect and sterilization of the blood. However, with the amounts of enzyme used there was found to be a degree of septicemia above which it was unable to control the infection, although the duration of life of the rabbits might be prolonged over that of control animals. Since excellent results had been obtained in the treatment of septicemia and local infections of the smaller animals, it seemed advisable to study the effect of the enzyme under conditions in which the disease more closely resembled that in the human patient suffering from pneumococcus pneumonia. In this disease, the organ involved is highly vital, the course is comparatively constant, the pathology typical, and recovery problematic. Consequently an attempt was made to produce in monkeys a disease resembling lobar pneumonia in man, which could then be subjected to treatment with the enzyme under conditions more closely approaching those encountered with patients in the hospital wards.

The Java monkey (M. cynomolgus) was used. The morphinized animal is placed in the supine position, and a small radio-opaque catheter is inserted into the trachea. With the aid of the fluoroscope, the catheter is then guided with direct visual control into the bronchioles of the lobe or lobules, in which the infection is desired. When the catheter is so placed, the bacteria are injected. The method has several advantages: First, it eliminates general anesthesia; second, the site of injection is known accurately; third, with better localization the number of bacteria required for infection is somewhat smaller, and the septicemia consequently tends to increase more gradually.

Throughout the study, temperatures were recorded 3 or 4 times daily and the course of the pneumonia was followed by daily roentgenograms.

Daily blood counts and blood cultures were made. In general, within 18 hours after inoculation, a definite well localized pneumonic consolidation can be seen in the X-ray. Concomitantly, a gradually rising fever is noted. The white blood cells may be increased in number, or, if septicemia is present, they may have decreased. The lesion continues to spread so as to involve the entire lobe and may extend to other lobes. The temperature remains elevated, the septicemia increases, and the leukocyte count tends to fall progressively. Death may follow in 4 to 7 days in the typical case. On the other hand, in a certain number of instances associated at times with either a diffuse infection of the lungs or with the well localized lesion, there is an immediate fall in leukocytes, a heavy septicemia and a tendency to subnormal temperature with a rapidly spreading lesion and an early fatal termination.

There is also a group of monkeys in which recovery takes place spontaneously after 3 to 7 days. In these, septicemia may be absent or slight in degree, although in two instances it has been comparatively high. The spontaneous recoveries occurring in this group make it difficult to speak of control animals in the usual sense, since the factor of individual variation, so far as we have been able to discover, cannot be allowed for. This is especially true when the purpose of the experiment makes a comparatively long, but gradually progressive and fatal course desirable. From the point of view of the production of pneumonia, of course, it does not matter, but when an attempt to evaluate a curative agent is made, the ideal is to approach absolute comparisons of treated and untreated animals. This has not been possible.

The studies to date include the results in 82 monkeys with definite pneumonic lobar consolidation of various degrees. Of these, 20 animals,

or 24.4 per cent, had no septicemia and all recovered. Twenty-three animals, 28 per cent, had rapidly mounting septicemia greater than 5,000 colonies per 1 cc. of blood in the first three days. All these animals died. The remaining animals were subdivided into two groups on the basis of the degree of septicemia present: (1) those in which septicemia was present but not greater than 250 colonies per 1 cc. of blood in the first 3 days; (2) those in which the septicemia ranged between 250 and 2,000 colonies in the first 3 days. The first of these two groups comprises 26 animals, or 31.9 per cent, and the second includes 12 animals, or 14.6 per cent. It is in these two groups that the conditions seem most favorable to study the possible effect of the enzyme upon the course of the experimental disease. The results obtained by treatment are tabulated below, comparing the mortality rate in a series of untreated animals with that of similar animals receiving treatment with the enzyme. The reason for dividing the groups on the basis of the first 3 days is that all of the animals treated received the enzyme in the first 3 days after inoculation.

Animals with pneumonia and septicemia less
than 250 col./cc. in first 3 days.

No. of animals		Recovered	Died	Mortality per cent
Untreated	Treated			
16		7	9	56.3
	10	10	0	0
Animals with pneumonia and septicemia from 250 to 2000 col./cc. in first 3 days.				
No. of animals		Recovered	Died	Mortality per cent
Untreated	Treated			
8		2	6	75
	4	4	0	0
Summary of both groups.				
No. of animals		Recovered	Died	Mortality per cent
Untreated	Treated			
24		9	15	63.1
	14	14	0	0

The results on the basis of comparative mortality figures are striking. In the animals of these groups which received treatment there have been no fatalities, whereas, well over 50 per cent of the untreated animals have succumbed. Five more animals were treated on the first day and one on the second day after inoculation. In these a definite consolidation was noted, in several the fever had reached 105° to 106° , and they seemed on a clinical basis to be suitable cases for the therapeutic test; however, at the time of treatment their blood cultures were sterile and remained so. They all recovered. Six others with very high initial septicemias were treated and although they all died, one treated on the first day with a septicemia of 18,000 colonies per cc. at that time did not die until the fifth day, and then with 2,000 colonies of Type III Pneumococcus per cc. Another with 25,000 colonies per cc. on the second day of disease lived until the fourth day, and at the time of death the septicemia had been reduced to 3,700 colonies per cc. This marked reduction of the number of bacteria in the circulating blood has been noted in others of the treated group in which death occurred early.

In addition to the effect of the enzyme on the septicemia, there is usually seen in the X-rays a definite prompt effect upon the pulmonic consolidation. The spread of the lesion is limited and the advancing margin begins to clear. At the same time, the fever tends to subside and the animal is alert and active, and takes interest in his food and surroundings. The immediate constitutional effect of the enzyme has varied with different preparations and with the severity of the disease. Some preparations have caused a fall in temperature and white blood count and have made the animals appear sicker. This is especially noted when the monkey is already very sick. In animals moderately sick there is a tendency to a febrile rise fol-

lowing treatment. It may be that the fall of the blood count is partially due to an increased mobilization of the leukocytes at the site of infection.

The treatment has usually consisted in the intravenous administration of 10 cc. of enzyme, varying from 2.5 to 20 units per cc. Following the original treatment, blood cultures and white counts are made and further treatment has been based on the results of these studies in conjunction with the general clinical appearance and the X-ray evidence. In some instances three treatments have been given in a period of 24 hours. In the later treatments the intraperitoneal route has sometimes been employed with satisfactory results, and perhaps some reduction in the amount of general reaction.

Although the study must be carried further, the results so far appear promising. Recently, it has been our privilege to move the monkey clinic to quarters which combine many features that tend to expedite the actual work. It is hoped that with more experimental animals, and with further improvement in technical procedures of concentration and purification of the enzyme, more potent and highly purified preparations may be available and that unequivocal results of its therapeutic effect may be obtained.